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LETTER TO THE EDITOR

Gamma-hydroxybutyrate (GHB) and topiramate - clinically relevant drug interaction suggested by a case with coma and increased GHB plasma concentration

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Gamma-hydroxybutyrate (GHB) and topiramate - clinically relevant drug interaction suggested by a case with increased GHB plasma concentration

To the Editor:

A 52-year-old woman was hospitalized for worsening chronic cluster headache refractory to all guideline-based medical and invasive treatments. Based on class IV evidence [1] she had regularly taken high-dose gamma-hydroxybutyrate (GHB, or also sodium oxybate; Xyrem[®]) 4.5 g twice-nightly at 11 pm and 3 am for the last 6 years. This was the only drug that markedly improved her nocturnal headache episodes and insomnia. As an additional therapeutic effort topiramate (Topamax[®]) was started with a single dose of 25 mg at 6 pm, and GHB was taken thereafter as usual. The next morning the patient developed confusion, followed by intermittent myoclonic jerks, miosis, and a rapid onset of coma with a Glasgow Coma Scale (GCS) score of 3 at 8:00 am. Pulse, blood pressure, respiratory rate, pulse oximetry, electrocardiogram and laboratory values including electrolytes and blood glucose were unremarkable. A blood sample for GHB determination using gas chromatography-mass spectrometry was obtained at 8 am, and its plasma concentration was 259 mg/L. One hour later electroencephalography (EEG) showed intermittent bifrontal theta activity, a pattern described during sedation with GHB [2]. At 1 pm the patient awoke from coma and rapidly recovered within a few hours. Topiramate was stopped, but GHB continued as before. Two days later GHB plasma concentration was measured again at 8 am and was 91 mg/L.

In the presented case, with concomitant topiramate GHB concentration 5 hours after its second dose was 2.8 times higher than without topiramate, and 1.8 times higher than a peak concentration of 142 mg/L that would be expected 0.5 to 2 hours after the second dose according to Xyrem[®]'s product information. In contrast, the patient had taken topiramate without concomitant GHB in the past without problems. Together with the rapid onset but

short duration of the otherwise unexplained coma and the EEG findings, this observation is highly suggestive of a drug-induced coma due to a pharmacokinetic interaction between GHB and topiramate. GHB has a short half-life of about 30 min [3], and metabolism via GHB-dehydrogenase is its main route of elimination [4]. In-vitro studies demonstrated inhibition of GHB-dehydrogenase by the antiepileptic drugs valproate and ethosuximide [4], but according to Xyrem[®]'s product information no interaction studies with antiepileptics were performed in humans. Alternatively, changes in the bioavailability of GHB or other unknown mechanisms of interaction are theoretically possible. Furthermore, topiramate increases GABA activity at its neuroreceptors, and an additional pharmacodynamic interaction must therefore also be considered.

In light of the increasing therapeutic as well as illicit use of GHB as well as of newer antiepileptic drugs, possible interactions should be evaluated in formal pharmacokinetic studies. Meanwhile we suggest using such combinations only with great care.

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